IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The application of	:	
Walter ELGER et al.	:	Group Art Unit: 1617
Serial No.: 09/744,574	:	Examiner: M. Bahar
Filed: 5 April 2001	:	

For: USE OF BIOGENIC ESTROGEN SULFAMATES FOR HORMONE REPLACEMENT THERAPY

BRIEF ON APPEAL

Honorable Commissioner of Patents
Washington, D.C. 20231

Sir:

Further to the Notice of Appeal filed on November 14, 2002, herewith are three copies of Appellants' Brief on Appeal. The attached check includes the statutory fee for the filing of this Brief and the necessary extension fee. The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

This is an appeal from the decision of the Examiner finally rejecting claims 8 through 17 of the above-identified application.

(1) REAL PARTY IN INTEREST

The real party in interest in the present application is JENAPHARM GMBH & CO.KG to whom the present application was assigned between January 15, 2001 and February 7, 2001 by 5 of the inventors, and Pekka Lähteenmäki and Matti Lehtinen (two of the inventors who have not assigned their rights to JENAPHARM GMBH & CO.KG by the time this Brief on Appeal is filed). The assignments have not yet been recorded. On information and belief, JENAPHARM is a wholly owned subsidiary of Schering, AG of Berlin, Germany.

I hereby certify that this correspondence is being deposited with the U.S. Postal Services as First Class Mail in an envelope addressed To: Commissioner of Patents and Trademarks, Washington, D.C. 20231 On: April 14, 2003
Name: Csaba Hoyer
Signature:
Date:

JENA-6

(2) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

(3) STATUS OF THE CLAIMS

Claims 8-17 are pending in the present application. Claim 17 contains an error. It should be dependent on claim 16 instead of on claim 15. An amendment is filed to correct this formal error.

(4) STATUS OF AMENDMENTS AFTER FINAL

Only the attached formal Amendment is filed after Final.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a method of achieving hormone replacement therapy in a woman by intermittently orally administering an estrogen sulfamate to said woman. The intermittent administration is in intervals of 2 or 3 days for a dosage of 20-300 μg/day, 5-10 days for a dosage of 0.5-5.0 mg/day, or 20-40 days for a dosage of 2.0-20 mg/day. See specification on page 1, lines 1-3, and page 13, last 5 lines on the page, to page 14, first two lines on the page.

(6) ISSUES

The issue presented for review is the rejections under 35 U.S.C. § 103(a), i.e., whether claims 8 to 17 are patentable over Siemann et al. (WO 96/05216) in view of Gale et al. (US 5,314,694).

(7) GROUPING OF THE CLAIMS

For the purpose of this appeal, all claims are considered to stand or fall together.

(8) APPELLANTS' ARGUMENTS

The 35 USC § 103 Rejection

The pending claims were rejected as allegedly unpatentable over Siemann et al. (WO 96/05216) in view of Gale et al. (US 5,314,694).

The current invention is not obvious over the cited references. Neither reference teaches or suggests, or provides motivation for, the intermittent oral administration of an estrogen sulfamate.

The Office Action dated May 14, 2003, appears to accept that these documents do not teach the intermittent oral administration of an estrogen sulfamate. However, the Office Action alleges that "variations and/or optimizations of the dosage regimen of compounds well known to be useful in HRT together sequentially or simultaneously are considered within the skill of the artisan." The rejection/allegation misses the point.

Whether it is totally routine to achieve intermittent administration is irrelevant. The question is not whether one could achieve intermittent administration, but whether the prior art teaches that those of skill in the art should use intermittent administration. There is no showing of the latter requisite. Thus, there is no obviousness.

Moreover, the alleged variations and/or optimizations necessary to achieve sequential or simultaneous administration are distinct from intermittent administration. The intermittent administration of estrogen sulfamates is not merely an optimization procedure when the prior art only teaches the daily administration of the same. The intermittent administration of the claims is entirely different.

WO '216 only teaches the daily administration of 10 micrograms per day of an estradiol, ethinyl estradiol, and estriol while also disclosing a generic formula that encompasses estriol-3-sulphamate. US '694 teaches the continuous administration of estrogen with norprogestrone. Based on the disclosure of the references, one of ordinary skill in the art would have understood that administration should be performed daily for the estrogen sulfamates as is taught for the other forms of the estrogen. Thus, one of ordinary skill in the art would have been only motivated to optimize the amount per day of said compound to be administered to a patient, assuming that the sulfamate form of the estrogen was chosen, for which also no specific motivation exists over the other disclosed species of the generic formula. No teaching or suggestion exists in the references that administration should be intermittently. Thus, one of skill in the art would not have been motivated to even try administering the estrogen sulfamates intermittently.

At the time this application was filed it was not obvious to one of ordinary skill in the art that estrogen sulfamates had good oral bioavailability and a half-life of estrogen release sufficiently long to make intermittent administration feasible.

The specification teaches that natural estrogens were known to be quickly eliminated from the blood, even in cases where oral administration is given daily, and that an increase of the dose by no means was a working mode for controlling the problem of strong fluctuations of the estrogen levels, i.e., fast elimination of the estrogens, from the blood. See specification on page 3 in its entirety and page 4, lines 1-4, and citations therein to Kuhnz et al. and Heithecker et al. The same is apparent from the Elger documents appearing on the Information Disclosure Statement filed on June 21, 2001. Especially see figures 9 and 10 from page 586 of the reference from Expert. Opin. Invest. Drugs showing that corresponding animal tests demonstrated that sulfamates released essentially all the estrogen after 24 hours. See also page 399 of the reference from J. Steroid Biochem. Molec. Biol. showing a dose determining study where only daily administration of estrogen sulfamates and other forms of estrogen were attempted for evaluation of the hepatic estrogenic activity of the hormones. One of skill in the art knowing that estrogens are quickly eliminated from the blood and that an increased dose does not overcome this problem would not only have lacked the motivation to try administering the estrogens intermittently, but would have had a prejudice against doing so.

The specification also teaches that the administration of estradiol sulfamate to ovarioectomized rats, while leading to prolonged and higher blood levels of estradiol and estrone than an equimolar dose of estradiol, did not result in an extension of the estrogen actions, even at very high doses. However, surprisingly, the release of the noted hormones form the sulfamate prodrug proceeded much more slowly in humans than in rats. No such teaching or suggestion is found in the prior art.

Additionally, applicants unexpectedly found that the period of estrogen release and hormone action could be affected by the level of the dose of the sulfamate prodrug of estrogen. Pharmacologically relevant blood levels were measured even after 4 weeks after a one-time administration. See specification on page 11, last 10 lines, and page 12, lines 1-5, the examples, and the figures. No such results could have been expected from the teachings of the prior art. why?

→ Applicants also found that uniform and well-defined levels of natural estrogens can be built up in the blood by the administration of the sulfamate prodrug of the estrogens. See specification on page 13, third full paragraph. Applicants submitted a figure with the Reply dated November 14, 2002, which was also submitted during the PCT proceeding which demonstrate the above-discussed phenomena. The figure shows a simulation of the

distribution of the biologically active main metabolite estrone in blood levels, shown in the accumulation of the estrone after the oral application of 2 mg estradiol sulfamate in weekly intervals in postmenstrual women. It is seen that maxima and minima of estrone in the blood levels increase up to the 4th or 5th application. This means, after the 4th or 5th application the relation between the maxima and minima is adjusted and is comparable with medicaments administered in 24 hour intervals. No such results could have been expected from the teachings of the prior art.

Based on these results, applicants found that, due to the slow release of the natural estrogens, in connection with a high oral bioavailability of the steroid portion of the administered estradiol sulfamate, administration can be conducted at larger intervals, i.e., can be conducted intermittently. No teaching or suggestion in the prior art references to this effect can be found, which would supply the requisite motivation to one of skill in the art to administer the estrogen sulfamates intermittently. Thus, the intermittent administration of estrogen sulfamate is not obvious based on the references. Additionally, as discussed above, the intermittent administration of an estrogen sulfamate is not merely an optimization of dosage regimen, but is a nonobvious procedure.

Conclusion

The claimed invention is not obvious because the cited prior art does not teach or suggest the intermittent administration of estrogen sulfamate to achieve hormone replacement therapy in a woman and because intermittent administration is not merely the optimization of the dosage regimen for estrogen sulfamate, but is instead an entirely new and nonobvious procedure. Thus, the reversal of the rejection is mandated by law, and is respectfully and courteously requested.

Respectfully submitted,

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APPENDIX

THE CLAIMS

8. A method of achieving hormone replacement therapy in a woman comprising intermittently orally administering an estrogen sulfamate at a dosage of 20-300 μg/day in intervals of 2 or 3 days; 0.5-5.0 mg/day in intervals of 5-10 days; or 2.0-20 mg/day in intervals of 20-40 days.

9. A method according to claim 8, wherein the estrogen sulfamate is estrone sulfamate, estradiol sulfamate, estriol sulfamate, N-acylsulfamate of estrone, estradiol or estriol having an acyl chain of up to 7 C atoms or mixtures thereof.

10. A method according to claim 8, wherein the intermittent oral administration is carried out at an interval of 2 to 40 days between administrations.

11. A method according to claim 8, wherein the intermittent oral administration is carried out at an interval of 5 to 10 days between administrations.

12. A method according to claim 8, wherein the intermittent oral administration is carried out at an interval of 2 to 3 days between administrations.

13. A method according to claim 8, wherein the intermittent oral administration is carried out at an interval of 20 to 40 days between administrations.

14. A method according to claim 8, further comprising the administration of a gestagen.

15. A method according to claim 14, wherein the at least one gestagen is levonorgestrel, desogestrel, norethisterone, medroxyprogesterone acetate, megestrol, cyproterone acetate, , chlormadinone acetate, dienogest, drospirenone or a mixture thereof.

16. A method according to claim 14, wherein the at least one gestagen is continuously administered.

*17. A method according to claim 16, wherein the continuous administration is in the form of an implant, in the form of an intrauterine release system or in the form of a combination thereof.

* Assumes entry of the accompanying amendment.